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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/533,512	05/02/2005	Maria Rosa Gasco	GASCO ET AL - 1PCT	4539

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EXAMINER	
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ART UNIT	PAPER NUMBER
1612	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/533,512	GASCO ET AL.	
	Examiner	Art Unit	
	GIGI HUANG	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 May 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11 and 22-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11 and 22-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. The response filed May 6, 2010 has been received, entered and carefully considered. The response affects the instant application accordingly:

   a. Claim 11 has been amended.

2. Claims 11, 22-28 are pending in the case.

3. Claims 11, 22-28 are present for examination.

4. The text of those sections of title 35.U.S. Code not included in this action can be found in the prior Office action.

5. All grounds not addressed in the action are withdrawn or moot.

Election/Restrictions

6. Claim 11 has been amended to be directed to an invention that is independent or distinct from the invention originally elected and claimed for the following reasons:

The newly amended claim 11 recites a method of treating particular ophthalmic disease comprising the intravenous or topical ocular administration of a pharmaceutical active incorporated into solid lipidic nanoparticles with steps utilizing and directed to the methods of manufacturing the solid lipid nanoparticle. The application had previously been subject to a restriction where unity was broken as lacking novelty between the method for treating of the ophthalmic disease with the solid lipid nanoparticle, the composition comprising the solid lipid nanoparticle, and the method of making the solid lipid nanoparticle. Applicant had elected the method of treating the condition with the SLN.

The newly amended claims if originally presented would have be subject to the restriction requirement and claims as amended constitutes an improper RCE/noncompliant response as the claims would be withdrawn based on the original election. However in an effort to advance prosecution for Applicant, the claims will be treated to the extent that as they read on the originally elected method of treatment with the SLN for the ophthalmic conditions as the amendment addresses the particular conditions for treatment, but will not examine the additionally added steps to the methods of making as it would constitute a new group. It is noted to Applicant that one of skill in the art to deliver the method of treatment (e.g. ophthalmologist) would not typically be in possession of the materials/machinery to manufacture the SLN's as written as they are traditionally found in chemical labs and manufacturing centers, rather than physician offices.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

7. Claims 11, 22-24, 27-28 are rejected under 35 U.S.C. 102(a) as being anticipated by Cavalli et al. (Solid lipid nanoparticles (SLN) as ocular delivery system for tobramycin).

Cavalli et al. teaches the use of solid lipid nanoparticles with tobramycin topically to the eye and expressly addresses it uses against bacterial endophthalmitis which

would be immediately envisioned. The particles had tobramycin at 2.5%w/w, stearic acid, an average particle size of 80nm, and 0.3mg was administered to each eye in rabbits weighing 2.8-3.5kg (suspension contained 0.3%w/v TOB).

All the critical elements are taught by the cited reference and thus the claims are anticipated.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 11, 22-28 are rejected under 35 U.S.C. 102(b) as being anticipated by Amselem et al. (U.S. Pat. 5662932).

Amselem et al. teaches pharmaceutical composition comprising emulsomes with a lipid core including solid lipid cores. The particles have a average particle size with preferred range of 10-250nm and in certain preparations the average will fall in the range of 50-150nm. The particles (emulsomes) can be administered in several ways including topically and intravenously. A particular mode of administration described in instillation into the eye and that these compositions are similar to those of parenteral solutions. Several drugs are taught to be used with the particles including beta-adrenergic blockers (e.g. adaprolol and timolol) for glaucoma, cannibinoids, antifungal, antibiotics, corticosteroids, AIDS drugs. The lipid for the core includes triglycerides such

as fatty acids in the C10-C18 range, tricaprin, trilaurin, trimyristin, tripalmitin, and tristearin. Other components that can be included are cholesterol and phospholipids.

Examples are provided with drug emulsomes with particles sizes and administered in different modalities were any ophthalmic condition in the posterior of the eye present would inherently be treated (e.g. Example 6 - 1% indomethacin with 0.5g indomethacin, 2.5g tricaprin, 0.1g cholesterol, 0.1g oleic acid, ophthalmic use; Example 16-18 adaprolol maleate (0.4%) topical to the eye for IOP reduction in rabbit with 2.5-3.0kg, Example 20- IV administration of HU-211 cannabinoid to rates at 5mg/kg particle average 153+/-24nm). It is noted that as the components of the composition are met, the properties of the composition are also met. Example 6 with 1% indomethacin with 0.5g indomethacin, 2.5g tricaprin, 0.1g cholesterol, 0.1g oleic acid is taught for ophthalmic use wherein it would inherently affect any condition affecting the posterior of the eye and also be immediately envisioned for its known uses in the eye (e.g. uveitis).

Example 17 also depicts the topical administration of the emulsomes comprising adaprolol maleate, tricaprin, cholesterol, and oleic acid for intraocular pressure (glaucoma) to the eye with a significant reduction of the IOP, wherein timolol would also be immediate envisioned as is known in the art as taught by Amselem. Example 20 depicts IV administration of HU-211 cannabinoid (known for anti-glaucoma) to rates at 5mg/kg wherein it would inherently affect any glaucoma present (Abstract, Col. 3 line 48-Col. 5 line 57, Col. 6 line 65-Col. 7 line 10, Col. 8 line 20-26, Col. 8 line 58- Col. 9 line 48, Col. 10 line 7-Col. 11 line 50, Examples, claims).

All the critical elements are taught by the cited reference and thus the claims are anticipated.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cavalli et al. (Solid lipid nanoparticles (SLN) as ocular delivery system for tobramycin) as applied above.

The teachings of Cavalli et al. are addressed above.

Cavalli et al. does not expressly teach an example of SLN with certain drugs such as hydrocortisone and timolol but does teach that these drugs and others ("hydrocortisone and progesterone, doxorubicin, paclitaxel, tobramycin, timolol, pilocarpine, etc") have been known to be previously incorporated in SLN's are known and administered by different routs including ocular and intravenous.

Cavalli also addresses that the use of SLN's with pilocarpine had improved ocular bioavailability and again with tobramycin; wherein it would be obvious to one of ordinary skill in the art at the time the claimed invention was made to utilize other drugs such as hydrocortisone and timolol in the SLN for ophthalmic delivery, and produce the

instant invention with a reasonable expectation of success and improved bioavailability as Cavalli teaches that SLN are a promising vehicle for topical ocular administration as they were well tolerated and drug levels were significantly higher with SLN's. Additionally Cavalli teaches that tobramycin (utilized in Cavalli), timolol (a known anti-glaucoma agent) as evidenced by Amselem, and hydrocortisone (known anti-inflammatory, e.g. uveitis) are known in the art to have been previously incorporated in SLN's and administered, wherein it would be obvious to utilize these drugs in SLN's for their known ophthalmic purposes.

One of ordinary skill in the art would have been motivated to do this because it is desirable to utilize drugs that have been previously placed in SLN's for their known ophthalmic purpose when previous work and evidence as addressed by Cavalli that the SLN forms have a better therapeutic profile and is well tolerated.

10. Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cavalli et al. (Solid lipid nanoparticles (SLN) as ocular delivery system for tobramycin) as applied above, in view of Schwartz (U.S. Pat. 4904649).

The teachings of Cavalli et al. are addressed above.

Cavalli et al. does not expressly teach intravenous delivery. Cavalli does however teach that many hydrophobic and hydrophilic drugs such as nifedipine, hydrocortisone, tobramycin, timolol, paclitaxel, and doxorubicin have been incorporated into SLN and SLN have been administered by several routes (e.g. parenteral, oral, ocular).

Schwartz teaches that corticosteroids such as hydrocortisone and beta-adrenergic such as timolol are used to treat glaucoma and can be administered in various ways including topically to the eye, orally, intravenously, and iontophoresis (Abstract, Col.5 line 48-52, Col. 6 line 14-33, 44-53).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to be used intravenously, as suggested by Schwartz, and produce the instant invention. It would have been obvious to one of skill in the art to utilize the SLN's taught by Cavalli for a known purpose in a known mode of administration as taught by Schwartz.

One of ordinary skill in the art would have been motivated to do this because Cavalli teaches that the SLN's have better therapeutic delivery, release, therapeutic profiles (bioavailability) whereby it would be desirable to use drugs known to be in SLN's for their known purpose for better results and therapy.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claim 11, 22-28 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 89 and 91 of copending Application No. 11/629141. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are more specific (species) and anticipate the broader claims (genus) of the copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

12. In regards to Applicant's assertion that the solid lipid nanoparticle of the invention can only have the chemical-physical properties to be used for treating the claimed ophthalmic conditions (bacterial or fungal endophthalmitis, viral retinitis, vitreoretinopathy, toxoplasmosis, uveitis, tumours, vascular diseases, diabetic retinopathy, age-related macular degeneration, and glaucoma), it has been fully considered but is not persuasive as it is unsupported by evidence or comparative evidence of the prior art. The prior art teaches the use of the solid lipid nanoparticle for the treatment of the same conditions listed in the claims (e.g. bacterial endophthalmitis, glaucoma) in the with same mode of administration.

13. Claims 11, 22-24, 27-28 are rejected under 35 U.S.C. 102(a) as being anticipated by Cavalli et al. (Solid lipid nanoparticles (SLN) as ocular delivery system for tobramycin).

Applicant's arguments filed 5/6/2010 have been fully considered but they are not persuasive. Applicant asserts that Cavalli does not identify ophthalmic diseases affecting the posterior art of the eye, treatment for the posterior part of the eye, or recite pharmacological actives for the treatment of these diseases. This is fully considered but not persuasive. Cavalli teaches that solid lipid nanoparticle comprising "hydrocortisone and progesterone, doxorubicin, paclitaxel, tobramycin, timolol, pilocarpine, etc " have been done and known in the art (Page 241), they have been administered by different routes including ocular (Page 241) and showed improved ocular bioavailability when tested with pilocarpine (Page 241) and also with tobramycin (Abstract). Cavalli also concludes that the SLN by topical ocular administration can treat bacterial endophthalmitis (Page 245). The assertion that there is no teaching for the posterior part of the eye is inaccurate as Cavalli teaches bacterial endophthalmitis which is a condition of the posterior segment of the eye as evidenced by Callegan et al. (see Page 111, Bacterial endophthalmitis-first sentence) contrary to the assertion that it is not in the posterior and despite being claimed. The assertion that only the SLN of the instant claims have the chemical-physical properties to be used for treating the claimed ophthalmic conditions (bacterial or fungal endophthalmitis, viral retinitis, vitreoretinopathy, toxoplasmosis, uveitis, tumours, vascular diseases, diabetic retinopathy, age-related macular degeneration, and glaucoma), is unsupported by

evidence or comparative evidence of the prior art. There also no evidence that the SLN of the claims and that of Cavalli are not the same. The prior art teaches the use of the solid lipid nanoparticle for the treatment of the same conditions listed in the claims (e.g. bacterial endophthalmitis, glaucoma) in the with same mode of administration.

Accordingly, the rejection is maintained.

14. Claims 11, 22-28 are rejected under 35 U.S.C. 102(b) as being anticipated by Amselem et al. (U.S. Pat. 5662932).

Applicant's arguments filed 5/6/2010 have been fully considered but they are not persuasive. Applicant asserts that Amselem does not identify ophthalmic diseases affecting the posterior art of the eye, treatment for the posterior part of the eye, or recite pharmacological actives for the treatment of these diseases. This is fully considered but not persuasive. Amselem teaches a solid lipid nanoparticle for ocular administration comprising actives such as indomethacin, HU-211, amphotericin B, corticosteroids, adaprolol, and timolol. Adaprolol and timolol are expressly taught for glaucoma treatment. Glaucoma is a condition of the posterior segment of the eye. It is a claimed condition wherein the use of a solid lipid nanoparticle comprising a known anti-glaucoma agent such as adaprolol and timolol for treatment with administration to the eye (claim 35, col. 10 line 7-20) as taught by Amselem fulfills the claims. The assertion that only the SLN of the instant claims have the chemical-physical properties to be used for treating the claimed ophthalmic conditions (e.g. glaucoma), is unsupported by evidence or comparative evidence of the prior art.

It is noted that Applicant asserts that glaucoma is a disease of the optic nerve wherein the ganglion cells die and that the intraocular pressure is one on the of risk factors; is not entirely accurate - glaucoma is not a disease of the optic nerve but is the condition, most commonly the high intraocular pressure, that is the cause of the deterioration of the optic nerve. Applicant also asserts that the drug is required to reach the optic nerve to be effective. This is not the case. Anti-glaucoma agents currently function by affecting and controlling intraocular pressure by utilizing one of two pathways-either reducing aqueous humor formation (inflow suppression, e.g. timolol) or improving the aqueous humor outflow (outflow enhancement). Some use both pathways (e.g. brimonidine), but they do not act on the optic nerve. Even attempts by others after the instant filing date address that there are no drugs that yet been shown to protect retinal ganglion cells (see Woodward et al.).

Accordingly, the rejection is maintained.

15. Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cavalli et al. (Solid lipid nanoparticles (SLN) as ocular delivery system for tobramycin) as applied above.

Applicant's arguments are directed to same issues as above and are addressed above. Applicant also argues direct accessibility to the posterior segment which is not persuasive as the same mode of administration (e.g. topical administration) is utilized wherein the same accessibility is present.

16. Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cavalli et al. (Solid lipid nanoparticles (SLN) as ocular delivery system for tobramycin) as applied above, in view of Schwartz (U.S. Pat. 4904649).

Applicant's arguments are directed to same issues Cavalli and are addressed above.

17. It is noted that Applicant argument Amselem et al. in the 103 heading but it is 102 rejection. In any case, the argument is that Amselem does not treat the disease only the worsening risk factor which is not persuasive as addressed above as it is not an accurate depiction of the known methods of the art nor an accurate depiction of the condition. In addition, treatment of the cause, symptoms, or side effects of a condition is by definition in the medicinal art, treatment of the condition. The argument by Applicant appears to be directed to a cure which is a different scope than treatment.

18. In regards to the declaration by Gasco, it has been fully considered but is not persuasive as the articles are directed to retinitis pigmentosa which is not a condition of the claims and states the utilization of particular commercially available serine palmitoyltransferase inhibitors which are not claimed and are not clear as to which compounds where utilized as it is well known in the art that not all compounds within a class will function in the same manner or efficacy for the treatment of conditions.

19. In response to applicant's general argument as it is not explicitly directed to a particular rejection, that there was no pertinent art at the time of the invention this is not persuasive as evidenced by the art rejection of record. As for the assertion of improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a

sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Wherein in the rejections above, there are clear directions given in the reference particularly for claim 11 wherein the teachings are for the SLN's for the same actives for treating the same conditions with the same mode of administration.

20. Claim 11, 22-28 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 89 and 91 of copending Application No. 11/629141.

There are no arguments, the rejection is maintained.

Conclusion

21. Claims 11, 22-28 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GIGI HUANG whose telephone number is (571)272-9073. The examiner can normally be reached on Monday-Thursday 8:30AM-6:00PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fredrick Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/GiGi Huang/
Examiner, Art Unit 1612
/Zohreh A Fay/
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